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ARTICLE

A general route to chiral nanostructures from helical polymers: P/M switch via dynamic metal coordination

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A general method for the conversion of a polyphenylacetylene into its *P* or *M* helically oriented polymer, and into their corresponding *P*/*M* helical nanoparticles via dynamic metal coordination is presented. Addition of M^{n+} ions (e.g., Ca^{2+}, Zn^{2+}, Ag^{+}, among others) to poly(phenylacetylene)s (poly-**2** to poly-**6**), bearing OMe protected amino acids, produce complex I (chelation of the two carbonyl groups; *sp* conformation) associated to a helix inversion of the polymer. Ulterior addition of a small amount of MeOH, transforms complex I into complex II (metal ion coordinated only to the ester group; *ap* conformation), where a second helix inversion is produced. This dynamic coordination proccess between complex I and complex II works also at the nanoscale level, and therefore chiral nanoparticles with either *P* or *M* helices can be generated or transformed into each other by controlling the polymer/metal/methanol ratio in the helical polymer metal complex (HPMC).

Introduction

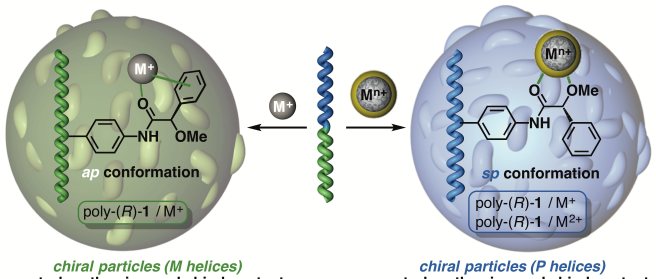
Chirality at the nanoscale has attracted the attention of the scientific community during the last decade due to the potential of chiral nanomaterials in fields related to sensing, chiral separation and nanoreactors among others.[1] The preparation of these novel nanostructures (fibres, nanospheres, nanotubes) has been explored using different families of building blocks that go from self-assembled small molecules,[2] to metal organic frameworks (MOFs),[3] dendrimers,[4] metal-peptide complexes[5] and polymer chains.[6]

In the last few years we have developed the preparation of macroscopically chiral nanospheres and nanotubes from helical polymer metal complexes (HPMCs),[7] derived from a dynamic poly(phenylacetylene)[8] bearing the anilide of the (*R*)-α-methoxy-α-phenylacetic acid (MPA) [poly-(*R*)-**1**] as pendant group. This is a privileged pendant due to its ability a) to complex mono and divalent metal ions in different way, and b) to transmit the structural characteristics of the complexed pendants to the polymer skeleton through a chiral amplification effect.[7-10]

Thus, while divalent metal ions chelate the carbonyl and methoxy group fixing the *sp* conformation at the pendant group (Scheme 1), the monovalent metal ions may coordinate the pendant in two different ways, depending on the amount of MeOH present in the $CHCl_3$ solution.

Hence, in the presence of small amounts of MeOH, the monovalent metal ion interacts with the amide carbonyl and with the aryl ring of the MPA moiety[10] (cation-π interaction), stabilizing the *ap* conformation (carbonyl and methoxy groups antiperiplanar oriented, Scheme 1). On the other hand, when the amount of MeOH is large, the cation-π interaction is disrupted and the monovalent metal ion coordinates the pendant group as divalent metal ions, stabilizing the *sp* conformation (Scheme 1). The different steric demands and bonding characteristics of those complexes is transmitted to the skeleton that adopts the more stable single-handed *P* or *M* helical structure.

Further advantages of this system are: a) the amount of metal ion needed to induce a single-handed *P* / *M* helical structure is very low, requires just a minute amount of the metal ion (chiral amplification effect) and, b) the metal ions can also act as crosslinking agents. Therefore, in the same operation we can control the helicity of the polymer and force it to aggregate into macroscopically helical nanospheres (Scheme 1).



Scheme 1: Chiral amplification and nanostructuration of poly-(*R*)-**1**/M^{n+} complexes.

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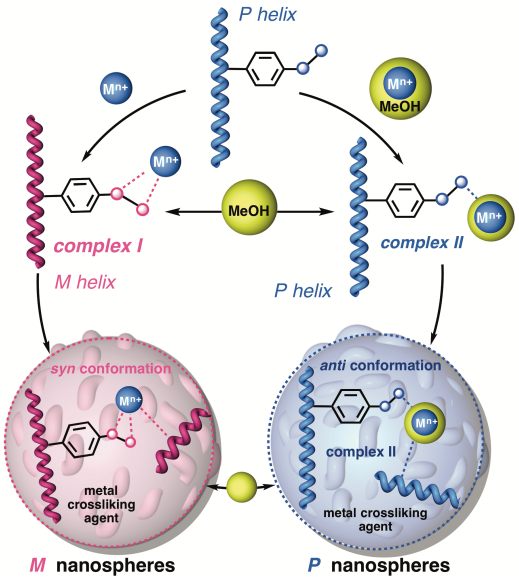
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [Synthesis monomers and polymers, thermal studies, IR measurements of different polymers, CD studies, nanostructuration studies, dynamic coordination and nanostructuration studies of poly-**2**/Ba^{2+} using different alcohols as cosolvents, supporting references]. See DOI: 10.1039/x0xx00000x

Unfortunately, this methodology for the conversion of a PPA into either *P* or *M* particles presents two limitations: 1) divalent metal ions coordinate the pendant group in a unique way, and therefore, only one helical sense is attainable from one polymer (e.g., *P* nanoparticles from poly-(*R*)-**1** and *M* from poly-(*S*)-**1**); 2) monovalent metal ions can form complexes in two different ways, leading to either *P* or *M* helices in the PPA, but transformation into nanospheres is limited to Ag^+, the only metal ion able to act both as effective crosslinking agent and helical inducer.

Results and discussion

In this paper, we present a general methodology that solves those limitations and allows selectively transforming a single PPA into the *P* or the *M* nanoparticles. Our approach consists on the use of a pendant with two distinct complexation sites that coordinate a metal ion in different ways modulated by an appropriate cosolvent: chelation of both coordinating groups to the metal ion or selective coordination of the metal ion towards each complexation site. Moreover, in these systems a) the structure of each complex leads to a certain helical sense, and b) one complex can be transformed into the other (*P* / *M* switch) by an external stimulus that changes their relative stability (e.g., a donor/polar cosolvent).

Scheme 2 illustrates this idea, showing a PPA (e.g., right-handed), which by addition of a $M(ClO_4)_n$ salt, is converted into a metal complex I, that favours the opposite helical sense (e.g., left-handed). This polymer metal complex I can be further transformed into a metal complex II (associated to right-handed sense), by the addition of a cosolvent that destabilises complex I and favours the formation of complex II. Moreover, if the metal ion could also work as crosslinking agent, nanostructures with either *P* or *M* helical senses could be selectively derived from the polymer complex.



Scheme 2: Helical sense control and selective of *M* or *P* nanostructuration by structural changes of the PPA/M^{n+} complex.

As complexation sites, we selected amide and ester functional groups (known to work well with M^{2+} in other PPAs) that were introduced into the pendants as 4-benzamides (amide complexation) of aliphatic amino acids [e.g., *L*-alanine (**2**), *D*-alanine (**3**), *L*-leucine, (**4**), *L*-isoleucine (**5**) and *L*-valine (**6**)] with the C termini protected by a methoxy group (ester complexation) (Figure 1).

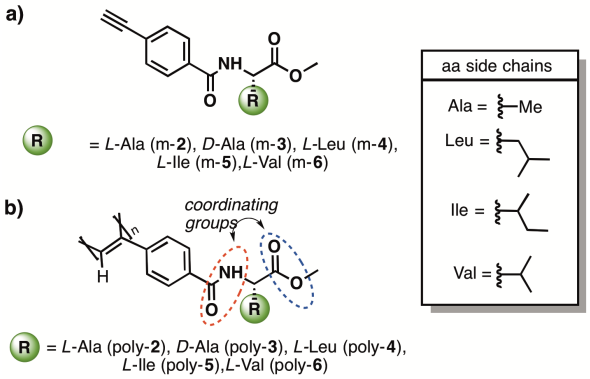


Figure 1: Structure of (a) monomers, m-(**2-6**) and (b) their corresponding PPAs, poly-(**2-6**).

In this way, the 4-ethynylbenzamide monomers of *L*-alanine methyl ester (m-**2**), *D*-alanine methyl ester (m-**3**), *L*-leucine methyl ester (m-**4**), *L*-isoleucine methyl ester (m-**5**) and *L*-valine methyl ester (m-**6**), were prepared and polymerized using $[\{Rh(nbd)Cl\}_2]$ as catalyst (nbd = 2,5-norbornadiene) producing poly-(**2-6**), in good yield (80-90 %) and with a high content of *cis* double bonds, (poly-**2:** vinyl protons at δ = 5.7–5.8 ppm, and Raman bands at 1582, 1340, 967 cm^{-1}), and a *cis-transoidal* backbone revealed by the presence in DSC of two isomerization bands at 190 °C (*c-t* to *c-c*) and 248 °C (*c-c* to *t-t*). Poly-(**3-6**) were shown to present quite similar data and structural characteristics (see ESI).[11]

The CD spectra of poly-**2** (0.3 mg mL^{-1}), shows a helical structure whose sense varies with the donor character of the solvent, e.g., poly-**2** present a first negative Cotton effect in $CHCl_3$ (Figure 2a) and positive in THF (Figure 3a), in accordance with the dynamic character of the polymer.[11] Poly-(**4-6**), showed the same CD signature as poly-**2** in $CHCl_3$, indicating that all those polymers share the same helical structure. As expected, poly-**3**, made from a *D*-amino acid, shows the opposite signature (see ESI for details).[12] It is important to note that since the PPA chains may contain fragments with left- or right-handed helical senses, the inversion of a CD sign does not necessarily mean complete switching of the helical sense but a change in the extend of biasing induced by the conformational changes at the pendant groups.

The addition of perchlorate salts of several metal ions (Ca^{2+}, Ba^{2+}, Mn^{2+}, Zn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Mg^{2+}, Fe^{2+}, Hg^{2+}, Ag^+, Li^+); (10 mg mL^{-1} in MeOH) to a $CHCl_3$ solution of poly-**2** (0.3 mg mL^{-1}) in a poly-**2** / M^{n+} / MeOH ratio= 1.0 / 0.2 / < 500 (mol / mol / mol) at room temperature, produced the immediate chelation between the metal ion and the carbonyls of the amide and ester groups of the pendant, as proven by IR, triggering the inversion of the original helical sense (Figure 2). This helix

inversion is due to the conformational change induced in the pendants by the formation of a complex that requires the *syn* orientation between the two carbonyls. Further additions of methanol to that solution [poly-**2** / M^{2+} / MeOH in a 1.0 / 0.2 / >500 mole ratio] produce another helical inversion and the recovery of the initial CD signature (Figure 2). At this point, IR indicates that the metal ion is still coordinated to the pendants but only to the ester group, stabilizing the *anti* conformation (Figure 2).

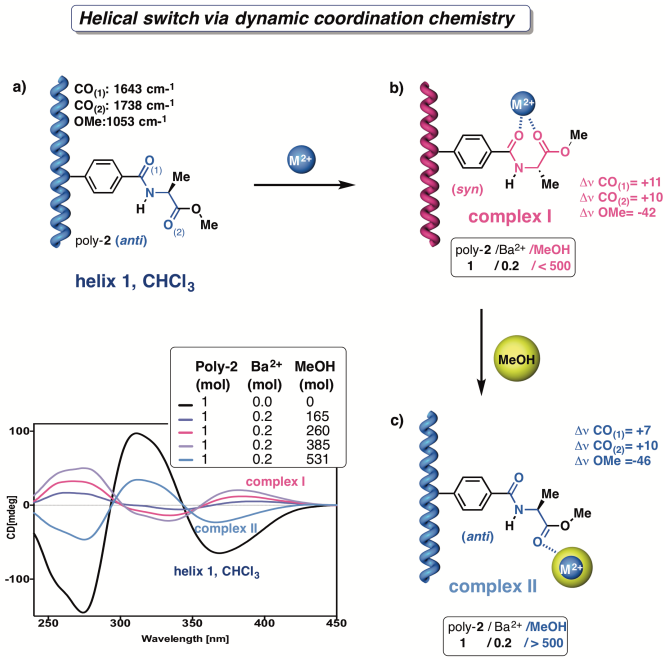


Figure 2: Helical switch of (a) poly-**2** ($CHCl_3$) —carbonyl groups *anti* oriented—, from right- to left-handed orientation of the polyene backbone after addition of (b) $Ba(ClO_4)_{2(MeOH)}$ salt in a (mru) / Ba^{2+} /MeOH ratio= 1 / 0.2 / <500 (mol / mol) —carbonyls *syn* oriented, complex I—. (c) Helix inversion of complex I after addition of methanol to form complex II [poly-**2** (mru) / Ba^{2+} / MeOH ratio= 1 / 0.2 / >500 (mol / mol / mol) —carbonyls *anti* oriented—]. [poly-**2**]= 0.3 mg mL^{-1} in $CHCl_3$, [$Ba(ClO_4)_2$]= 10 mg mL^{-1} in MeOH. Helical switch supported by CD and IR data [$\Delta\upsilon$ indicates the difference between the IR band for a complex structure (I or II) minus the initial one from the non-complexed polymer].

Complexation studies on poly-(**3**-**6**) showed the same dynamic coordination mechanism to the one observed for poly-**2**. Thus, an initial helix inversion is induced in the polyene skeleton due to the formation of complex I, followed by a second inversion produced by addition of MeOH and formation of complex II. A partial exception was found in poly-**6**, where the addition of MeOH to evolve complex I into complex II, is not accompanied by helix inversion. In this case, poly-**6** is sensitive to MeOH, inverting its helical sense with minute amounts of this solvent. As a result, the helical structure is governed by the solvent and not by the dynamic coordination chemistry (see ESI, Figures S16-S21).

UV experiments showed that, in all cases, the chelation of the metal ion to the pendant group produced a slight bathochromic effect in the structure of both complexes (complex I and II) to accommodate the metal into the helical scaffold (see ESI, Figures S16-S21).

In order to demonstrate the relationship between the conformational changes at the pendant group and the chelation mode of the metal ion (*anti* in the free polymer, *syn* in complex I and *anti* in complex II), we decided to repeat the experiments in a donor solvent as THF, where poly-**2** adopts a native *syn* conformation (negative CD in $CHCl_3$ and positive in THF; Figure 3a). In this case, addition of the metal ion should not produce changes in the conformation of the pendants or in the helix because the carbonyl groups involved in chelation are already in *syn* conformation.

Figure 3b confirms this prediction, showing that the addition of Ba^{2+} to poly-**2** in THF (poly-**2** / M^{2+} / MeOH mole ratio: 1.0 / 0.2 / 165) at room temperature produced no changes in the CD, although complex I was formed (Figure 3c). Moreover, it was also found that increasing the amount of MeOH [poly-**2** / M^{2+} / MeOH ratio = 1.0 / 0.2 / >500 (mol / mol / mol)] leads to a complexation change, from complex I (metal coordinated to amide and ester groups) to complex II (metal coordinated to ester group), but without changes in the helicity (Figure 3d).

Thus, these studies demonstrate that chelation of these HPMCs is associated in all cases (complex I and II) to a *syn* conformation. An important consequence from this evidence is that only PPAs with a native *anti* conformer will show helical inversion upon addition of the metal ion, and further inversion by addition of MeOH.

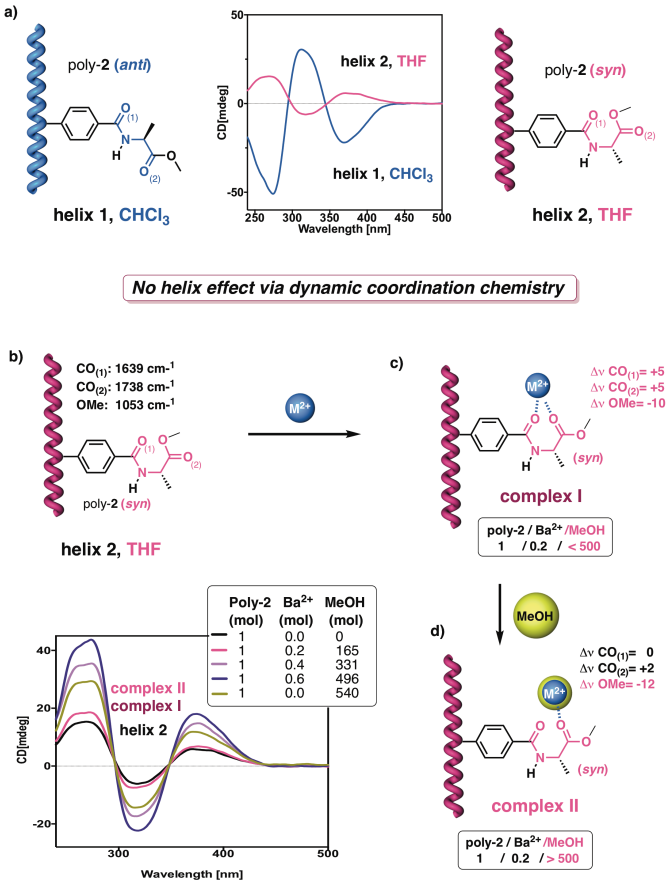
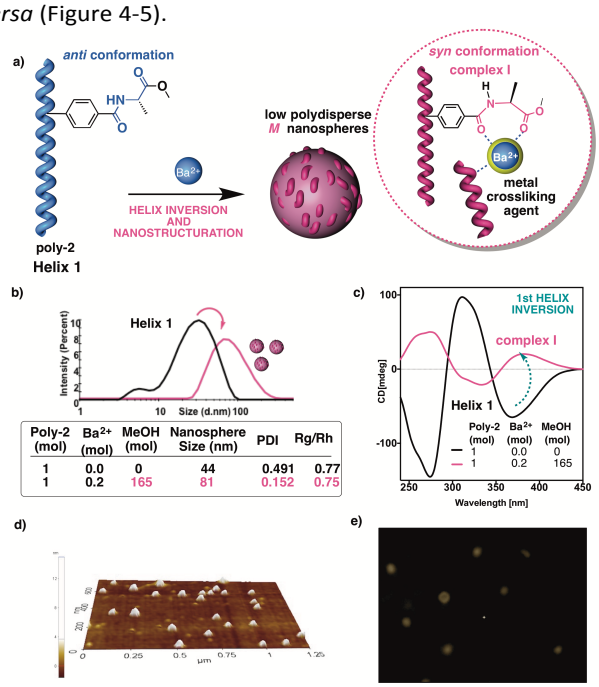


Figure 3: a) CD spectra of poly-**2** in $CHCl_3$ and THF showing helical structures with opposite helical sense. No helical switch observed between (b) poly-**2** (0.3 mg/mL THF), (c) complex I [poly-**2** / M^{2+} / MeOH ratio = 1.0 / 0.2 / <500 (mol / mol / mol)] and complex II [poly-**2** / M^{2+} / MeOH ratio = 1.0 / 0.2 / >500 (mol / mol / mol)]. Dynamic coordination chemistry supported by IR data where $\Delta\upsilon$ indicates the difference between the IR band for a complex structure (I or II) minus the initial one from the non-complexed polymer.

Once we knew how to control helical inversion by dynamical switching from complex I to complex II, we turned our attention to explore the aggregation of HMPCs to form the corresponding *P* or *M* helical nanostructures. Moreover, we wanted also to explore the dynamic helical behaviour at the nanoscale level, transforming *P* into *M* nanospheres and *vice versa* (Figure 4-5).



Poly-2 (mol)	Ba^{2+} (mol)	MeOH (mol)	Nanosphere Size (nm)	PDI	Rg/Rh
1	0.0	0	44	0.491	0.77
1	0.2	165	81	0.152	0.75

Figure 4: Conceptual representation of *M* nanostructuration of the poly-**2**/Ba^{+} complex in $CHCl_3$ through dynamic coordination chemistry, c) CD spectra showing the helix inversion of poly-**2** (0.3 mg mL^{-1} $CHCl_3$) by the presence of $Ba(ClO_4)_2$ (10 mg mL^{-1} MeOH) to form the [poly-**2**(mru) / Ba^{2+} / MeOH complex in a 1.0 /0.2 / <500 (mol / mol / mol) ratio, (b, d) left-handed nanospheres (diameter= 75 nm ± 6, 8 particles, scale bar 300 nm) prepared in a poly-**2**(mru)/Ba^{2+}/MeOH ratio= 1.0 / 0.2 / 165 (mol / mol / mol) and e) Confocal image of chiral nanospheres with encapsulation properties (QDots) made from a left-handed helical structure (see ESI for more information).

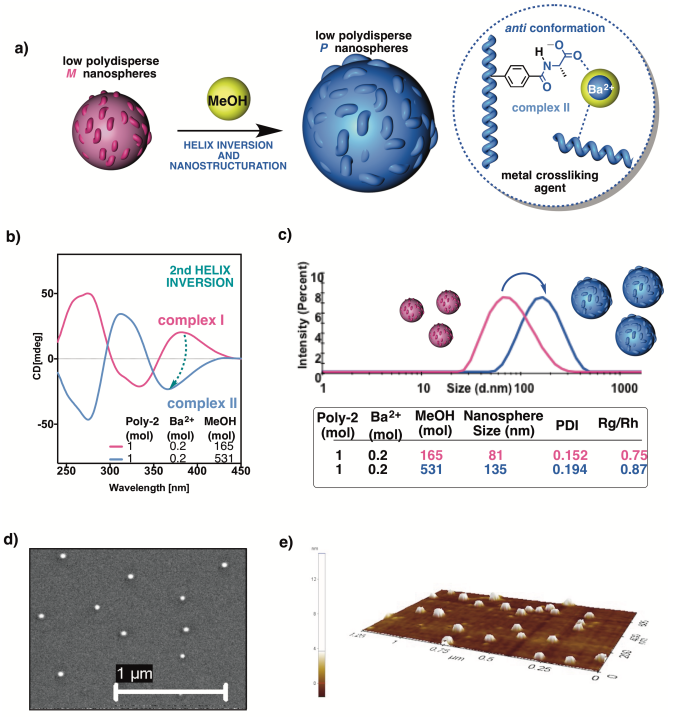
Thus, addition of barium perchlorate (10 mg mL^{-1} of MeOH) to a $CHCl_3$ solution of poly-**2** (0.3 mg mL^{-1}) in a poly-**2** / M^{2+} / MeOH in a ratio= 1.0 / 0.2 / 165 (< 500) (mol / mol / mol) —complex I—, produced immediately, at room temperature, well-defined, stable and with low polydispersity *M* nanospheres of 81 nm diameter (PDI = 0.152) (Figure 4b-c). Further addition of MeOH until a poly-**2** / M^{2+} / MeOH ratio: 1.0 / 0.2 / 531 (>500) (mol / mol / mol) —complex II—, produced well-defined enantiomeric *P* nanospheres (135 nm, PDI = 0.194) (Figure 5b-c).

The size, shape and stability of these nanospheres were checked in solution and in the solid state by DLS and microscopy studies (SEM, AFM, Confocal) (Figure 4d-e and Figure 5d-e). Moreover, their encapsulation ability was demonstrated with quantum dots (QDs), rhodamine B and fluorescein. (Figures 4e and S28).

This nanostructuration was also observed for poly-**3** and poly-**4,** using a large variety of metal ions as Ca^{2+}, Ba^{2+}, Mn^{2+}, Zn^{2+}, Co^{2+}, Ni^{2+}, Fe^{2+}, Cu^{2+}, Ag^{+}, Li^{+} (see ESI), exhibiting the robustness of the PPA-aa-OMe / metal ion complex system to produce nanospheres with controlled and tuneable helicity. In the particular case of pendants with beta branched amino acids (poly-**5** and poly-**6**), the steric hindrance reduces or totally disrupts the crosslinking ability of the metal and therefore chiral nanospheres cannot be obtained (see Figures S23-S25).

Finally, we decided to test the role played by the structure of the alcohol used as cosolvent in the dynamic coordination chemistry and nanostructuration of a poly-**2**/Ba^{2+} complex. Thus, we selected ethanol, propanol, isopropanol and *tert*-butanol to perform our studies. Unfortunately, $Ba(ClO_4)_2$ is soluble only in ethanol, and therefore we could only perform a complete set of experiments with the poly-**2**/Ba^{2+}/EtOH system, that was also generated using the procedure describe below for other alcohols. Poly-**2**/Ba^{2+}/EtOH produced almost identical results to the ones obtained from poly-**2**/Ba^{2+}/MeOH, that is, EtOH induces the formation of complex II keeping the crosslinking ability of Ba^{2+} to form low polydisperse nanospheres.

To determine the effect of the larger alcohols into the poly-**2**/Ba^{2+} complex, we first prepared complex I using MeOH as cosolvent. Next, it was transformed into complex II by adding the different alcohols (i.e., propanol, isopropanol and *tert*-butanol). Interestingly, we found that higher ratios of these alcohols, bearing larger or branched alkyl chains, are needed to transform complex I into complex II when compared to MeOH or EtOH ratios. Moreover, with these more hindered alcohols, the crosslinking ability of the metal is disrupted and accordingly, nanospheres are not generated (see Figure S31).



Poly-2 (mol)	Ba^{2+} (mol)	MeOH (mol)	Nanosphere Size (nm)	PDI	Rg/Rh
1	0.2	165	81	0.152	0.75
1	0.2	531	135	0.194	0.87

Figure 5: Conceptual representation of *P* nanostructuration of the poly-**2**/Ba^{+} complex in $CHCl_3$ through dynamic coordination chemistry, b) helix inversion of poly-**2**(mru)/Ba^{2+}/MeOH complex in a 1.0 / 0.2 / <500 (mol / mol / mol) ratio by addition of MeOH until reach a poly-**2**(mru) / Ba^{2+} / MeOH ratio of 1.0 / 0.2 / >500. DLS and SEM, AFM images showing (c, d, e) right-handed nanospheres (diameter= 72 nm ± 9, 10 particles, scale bar 1 µm) prepared in a poly-**2**(mru) / Ba^{2+}/MeOH ratio= 1.0 / 0.2 / 531 (mol / mol / mol) (see ESI for more information).

Conclusions

The introduction of an amide and an ester group into the pendant moiety of a PPA (e.g., PPA-aa-OME of aliphatic amino acids), poly-**2** to poly-**5**, allows the formation of two different complexes with mono- and divalent metal ions, –complex I and II— controlled by the amount of a cosolvent (MeOH). Thus, in the presence of small amount of MeOH, the metal ion chelates both carbonyl groups to form complex I, that induce in the PPAs of natural amino acids (*L*-series, poly-**2**,**4**-**5**) a left-handed helical structure into the polymer, and the formation of *M* nanospheres. On the other hand, when the amount of MeOH is larger, the coordination of the metal ion changes to complex II, with the metal ion linked only to the ester group, inducing the *P* helical sense in the PPA and the formation of *P* nanospheres**.** Therefore, this dynamic coordination process (from complex I to complex II) works not only on the polymer, but also at the nanoscale level, and nanospheres with *P or M* helical sense can be transformed into the helically enantiomeric *M* or *P* particles with MeOH.

Selective encapsulations of chiral molecules (e.g., drugs, biomolecules) or their use as chiral nanoreactors for asymmetric synthesis, etc., are some of the potential applications envisioned for the above or related chiral nanospheres.

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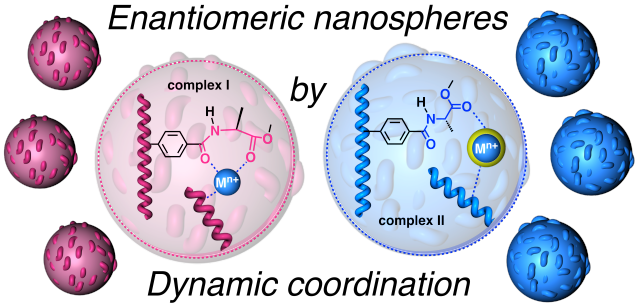
TOC



Macroscopically enantiomeric chiral nanospheres made by *P* or *M* helical polymer metal complexes can be obtained via dynamic coordination chemistry